# Cervicography screening for cervical cancer among 8460 women in a high-risk population

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**OBJECTIVE:** Cervicography was evaluated as a primary screening method for cervical cancer.
**STUDY DESIGN:** Cervigrams of 8460 women were taken on enrollment into a population-based study of cervical neoplasia. Cervicography results were compared with a referent diagnosis determined by histologic analysis and 3 cytologic tests, and with the performance of conventional cytologic evaluation.
**RESULTS:** Cervicography identified all 11 cancers, whereas cytologic testing missed 1. Cervicography yielded sensitivities for detecting high-grade squamous intraepithelial lesions or cancer of 49.3% overall (specificity, 95.0%), 54.6% in women younger than 50 years of age, and 26.9% in women 50 years of age and older. Cytologic testing yielded sensitivities for detecting high-grade squamous intraepithelial lesions or cancer of 77.2% overall (specificity, 94.2%), 75.5% in women younger than 50 years of age, and 84.6% in women 50 years of age and older.
**CONCLUSIONS:** Cytologic testing performed better than cervicography for the detection of high-grade squamous intraepithelial lesions. Cervicography performed marginally better than cytologic testing for the detection of invasive cervical cancer. Cervicography is not recommended for postmenopausal women. (Am J Obstet Gynecol 1999;180:290-8.)

**Key words:** Cervicography, cervical cancer, screening, visual, cervix

Cervical cancer incidence and mortality rates have markedly declined over recent decades in countries that have implemented widespread cytologic screening using the Papanicolaou smear.[1-3] However, the Papanicolaou smear, like any other screening method, is not a perfect tool. Cytologic screening failures may reflect inadequate sampling, poor slide preparation, or errors in microscopic screening or diagnosis.[4-6] Concerns about errors in conventional Papanicolaou smears have motivated some researchers to evaluate alternate or adjunctive screening methods.[7-10]

The present analysis was conducted to provide a rigorous and independent evaluation of cervicography (National Testing Laboratories Worldwide, Fenton, Mo) as a primary screening method for early identification and prevention of cervical cancer. In this analysis, 8460 cervigram results are compared with a "gold standard," referent diagnosis based on histologic evaluation and 3 cytologic methods. As a point of reference, cervicography is also compared with conventional cytologic screening.

## Material and methods

This study of cervicography was conducted as part of a large, population-based study of the natural history of cervical neoplasia in Guanacaste Province, Costa Rica. The study design is described in greater detail elsewhere.[11] The protocol for this study was approved by the Costa Rican and National Cancer Institute Institutional Review Boards.

**Subject selection and participation rates.** The cohort

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***6/1/94201***

**Table I.** Cervigram diagnostic classification

| | |
|---|---|
| Not referred for colposcopy | |
| Negative | No lesion seen |
| Atypical 1 (A1) | A trivial lesion inside the transformation zone is visible, but colposcopy is not recommended because of the benign appearance or site of the lesion |
| Atypical 2 (A2) | A trivial lesion outside the transformation zone is visible, but colposcopy is not recommended because of the benign appearance or site of the lesion |
| Technically defective | Unable to be properly evaluated |
| Referred to colposcopy | |
| Positive 0 (P0) | Probably normal, but colposcopy preferable to rule out serious neoplasia |
| Positive 1A (P1A) | Compatible with trivial disease, but colposcopy recommended because part of the lesion extends into the canal |
| Positive 1B (P1B) | Compatible with a low-grade squamous intraepithelial lesion, flat condyloma, and exophytic condyloma |
| Positive 2 (P2) | Compatible with a high-grade squamous intraepithelial lesion |
| Positive 3 (P3) | Compatible with cancer |

was enrolled between June 1993 and December 1994. The population was recruited through door-to-door visits in randomly selected census segments. A total of 11,742 women was selected who met the initial eligibility criterion of being 18 years of age or older by July 1,1993. Of those, 10,738 (91.5%) were eligible for an interview. Women who were not Guanacaste residents or who were mentally incompetent, physically incapacitated, unable to understand Spanish, or deceased were excluded.

Study clinics were established at regional hospitals or at dozens of local health outposts. Pregnant women were deferred until 3 months after giving birth. A total of 10,049 of the 10,738 eligible women (93.6%) was interviewed. Pelvic examinations were not performed on the 583 virgins who completed the enrollment interview. The remaining 9466 (94.2% of those interviewed) were eligible for an enrollment pelvic examination. Of those, 291 women either refused or were physically unable to undergo the pelvic examination. Pelvic examinations were performed on 9175 women, and a referent diagnosis was established for all of these. Cervigrams were obtained for 9062 women, corresponding to 98.8% of women who completed the pelvic examination. The 602 women who had undergone hysterectomy (6.6%) were subsequently excluded from the analyses, leaving 8460 participants available for the study.

**Clinical specimens.** After obtaining informed consent, patients participated in a detailed interview to assess risk factors for cervical neoplasia and then underwent a routine pelvic examination. Cervical cytologic and human papillomavirus (HPV) deoxyribonucleic acid (DNA) specimens were collected during the pelvic examinations using a Cervex Brush (Unimar, Wilton, Conn). Two types of cytologic preparations were made for each participant, including a Papanicolaou smear and a ThinPrep (Cytyc, Boxborough, Mass). Papanicolaou smears were fixed with Pap Perfect (Medscand, Hollywood, Fla) and were later stained by the Papanicolaou method in Costa Rica. After the smear was made, the Cervex brush was rinsed in 20 mL of PreservCyt (Cytyc). Vials containing the PreservCyt solution were sent to the United States, where ThinPreps were made.

Additional cervical cells were collected using a Dacron swab, which was placed in Specimen Transport Medium (Digene Corp, Silver Spring, Md), frozen, and shipped to the United States for HPV DNA testing using the first-generation Hybrid Capture tube test (Digene). Samples were tested for HPV positivity at the 10 pg/mL level[12] using probes for cancer-associated types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58) and low-risk types (6, 11, 42, 43, and 44).[13, 14]

The cervix was then rinsed with 5% acetic acid, and 2 photographic images of the cervix (Cervigrams) were taken using a Cerviscope (National Testing Laboratories Worldwide). The undeveloped film was sent to the United States for developing, processing, and evaluation.

**Cervigram review.** Cervigrams were interpreted by certified evaluators (M.D.G. and T.V.S.) and classified according to the diagnostic criteria approved by National Testing Laboratories Worldwide as noted in Table I.

**Cytologic diagnosis.** Cytologic diagnosis was made using 3 methods: Papanicolaou smear, PapNet (Neuromedical Systems, Inc, Suffern, NY), which uses the same slide as the Papanicolaou smear; and ThinPrep. Papanicolaou smears were interpreted in Costa Rica (M.A.). ThinPreps were prepared and interpreted in the United States (M.L.H.). After interpretation in Costa Rica, all available Papanicolaou smear slides were sent to Neuromedical Systems for repeat screening using the PapNet system, a neural network–based, semiautomated device.[9] Papanicolaou smear, ThinPrep, and PapNet results were classified according to the Bethesda System as negative (within normal limits or reactive cellular changes), atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, or carcinoma.[15]

**Colposcopic referral, biopsy, and management.** Participants were referred for colposcopy (1) if physical examination was suspicious for cancer, (2) if there was an abnormal cytologic result by any of the 3 methods (atypical squamous cells of un-

**Table II.** Referent case diagnoses

| | |
|---|---|
| Cancer | Histologically confirmed invasive cancer |
| HSIL | Histologically confirmed HSIL |
| HSIL2 | Women with a conventional Papanicolaou smear and/or PapNet result of HSIL, plus a ThinPrep result of HSIL, but no histologic confirmation |
| LSIL | Histologically confirmed LSIL |
| LSIL2 | Women with no histologic confirmation of a squamous intraepithelial lesion and at least 2 of the following criteria met: (1) a conventional Papanicolaou smear or PapNet result of LSIL; (2) a Thin Prep diagnosis of LSIL; or (3) a cervigram result of P1, P2, or P3 |
| Equivocal—NL/HSIL | Women with a differential diagnosis of HSIL versus negative on final review (severe atrophy contributed to this diagnostic category) |
| Equivocal—NL/LSIL | Women whose overall results were equivocal, even after review by the chief study pathologist |
| Equivocal/ThinPrep | Women with a ThinPrep cytologic diagnosis of LSIL and all other screening tests normal |
| Equivocal/Papanicolaou | Women with either a conventional Papanicolaou smear or PapNet diagnosis of LSIL and all other screening tests normal |
| Equivocal/cervigram | Women with a cervigram result of P0, P1, P2, or P3 and no cytologic or histologic confirmation |
| Normal2 | Women referred to colposcopy with a cytologic diagnosis of atypical squamous cells of undetermined significance who were normal after review |
| Normal | Women with all negative screening results |

*LSIL,* Low-grade squamous intraepithelial lesion; *HSIL,* high-grade squamous intraepithelial lesion.



determined significance or more severe), or (3) if there was a positive cervigram. Colposcopy was performed by a single gynecologist (J.M.). Biopsies of lesions visualized on colposcopy were fixed in 10% buffered formalin, embedded in paraffin, stained with hematoxylin and eosin, and diagnosed in Costa Rica for clinical purposes. Histologic material, including punch biopsies, subsequent cone biopsies, excised tissue, and hysterectomies, was sent to the United States for review and assignment of the referent diagnosis (M.E.S.). Participants with histologically confirmed high-grade squamous intraepithelial lesions or cancer, or with a highly suspect diagnosis of high-grade squamous intraepithelial lesion (by at least 2 cytologic methods), were referred for treatment through the Costa Rican Social Security system.[11]

As a quality control measure, a random sample of 2% of all women was referred for colposcopy to validate the screening protocol. All 144 of the women with all negative screening tests had a referent diagnosis of normal, indicating 100% sensitivity of the screening protocol.

**Referent diagnosis.** Referent diagnoses were made based on histologic, cytologic, and cervicography results and were classified as indicated in Table II, with subsequent "lumping" as required for the data analysis.

**Data analysis.** Sensitivity and specificity of cervicography were calculated with the referent diagnosis as the gold standard. Sensitivity is defined as the proportion of participants with "disease" who are diagnosed by the screening method under evaluation. Specificity is defined as the proportion of participants without "disease" who are correctly identified as being free of disease using the screening method under evaluation. Two different definitions of *disease,* based on referent diagnoses, were used as targets for screening: (1) Disease is high-grade squamous intraepithelial lesion or cancer (vs normal, equivocal, or low-grade squamous intraepithelial lesion); (2) disease is low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, or cancer (vs normal or equivocal). Two thresholds to define a positive cervigram result were examined for analytical purposes including (1) positive is P0, P1, P2, or P3 (vs atypical or negative) and (2) positive is atypical or more severe (vs negative).

When presenting detection of low-grade squamous intraepithelial lesions, we refer to the percentage of patients referred for colposcopy rather than specificity because, given what is currently known about the dynamic nature of HPV infection,[16] diagnostic techniques are not available to adequately confirm that no low-grade squamous intraepithelial lesion is present. The percentage referred provides us with a proportion that will be correlated with the false-positive rate and will permit trade-offs with sensitivity.

Analyses of sensitivity and specificity were conducted using standard contingency table methods. Tables were stratified by age and factors related to pregnancy history, menopausal status, smoking history, and oral contraceptive use to assess whether any of these factors affected the performance of cervicography.

Cervicography was directly compared with conventional cytologic screening based on the threshold level for colposcopic referral. Discordant results are described by the referent diagnosis and by an independent measure, the presence of cancer-associated HPV types. Differences between the proportions of women referred for colposcopy by cervicography and cytologic evaluation among those with a referent diagnosis of high-grade squamous intraepithelial lesion or cancer, and among women who had a positive test result for cancer-associated HPV types, were assessed for statistical significance using McNemar's test for paired data.

## Results

**Cervicography screening compared with referent diagnosis.** The distribution of referent diagnoses by cervigram results are presented in Table III. Of the 8460

**Table III.** Distribution of the referent diagnosis by cervigram result

| | *Final diagnosis†* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Cervigram result** | *Normal (No., %)* | *Equivocal (No., %)* | *LSIL2 (No., %)* | *LSIL (No., %)* | *HSIL2 (No., %)* | *HSIL (No., %)* | *Cancer (No., %)* | *Total (No., %)* |
| Technically defective | 103 | 6 | 0 | 1 | 2 | 1 | 0 | 113 |
| | 1.4 | 0.8 | 0.0 | 1.4 | 25.0 | 0.9 | 0.0 | 1.3 |
| Negative | 6560 | 316 | 71 | 15 | 6 | 42 | 0 | 7010 |
| | 88.5 | 43.7 | 61.7 | 20.3 | 75.0 | 35.9 | 0.0 | 82.9 |
| Atypical 1 | 147 | 5 | 2 | 1 | 0 | 2 | 0 | 157 |
| | 2.0 | 0.7 | 1.7 | 1.4 | 0.0 | 1.7 | 0.0 | 1.9 |
| Atypical 2 | 595 | 53 | 18 | 14 | 0 | 16 | 0 | 696 |
| | 8.0 | 7.3 | 15.7 | 18.9 | 0.0 | 13.7 | 0.0 | 8.2 |
| Positive 0 | 1 | 134 | 2 | 2 | 0 | 2 | 3 | 144 |
| | <0.1 | 18.5 | 1.7 | 2.7 | 0.0 | 1.7 | 27.3 | 1.7 |
| Positive 1A | 0 | 63 | 6 | 5 | 0 | 5 | 0 | 79 |
| | 0.0 | 8.7 | 5.2 | 6.8 | 0.0 | 4.3 | 0.0 | 0.9 |
| Positive 1B | 2 | 130 | 16 | 31 | 0 | 32 | 0 | 211 |
| | <0.1 | 18.0 | 13.9 | 41.9 | 0.0 | 27.4 | 0.0 | 2.5 |
| Positive 2 | 1.0 | 11 | 0 | 5 | 0 | 12 | 3 | 32 |
| | <0.1 | 1.5 | 0.0 | 6.8 | 0.0 | 10.3 | 27.3 | 0.4 |
| Positive 3 | 2 | 6 | 0 | 0 | 0 | 5 | 5 | 18 |
| | <0.1 | 0.8 | 0.0 | 0.0 | 0.0 | 4.3 | 45.5 | 0.2 |
| TOTAL | 7411 | 724 | 115 | 74 | 8 | 117 | 11 | 8460 |

*LSIL*, Low-grade squamous intraepithelial lesion; *HSIL*, high-grade squamous intraepithelial lesion.
*Cervigram classification scheme is provided in Table I.
†Definitions of the referent diagnosis are provided in Table II.

women who had a cervigram, 484 (5.7%) had a positive cervigram result and were referred for colposcopy. All 11 cases (100%) of invasive cancer were detected by cervicography. Of these critical cases, 3 (27.3%) had a cervigram result of positive 0, 3 (27.3%) had a cervigram result of positive 2, and 5 (45.5%) had a cervigram result of positive 3. In 6 of the 11 women with cancer (54.5%), a grossly visible lesion was identified on physical examination, which in itself prompted colposcopy referral.

Of the 125 cases of high-grade squamous intraepithelial lesions on referent diagnosis, 117 were histologically confirmed and 8 were confirmed by cytologic testing only (high-grade squamous intraepithelial lesion 2). Of the histologically confirmed cases of high-grade squamous intraepithelial lesions, 56 (47.9%) were detected by cervicography, including 2 (1.7%) with a positive 0 cervigram, 5 (4.3%) with a positive 1A cervigram, 32 (27.4%) with a positive 1B cervigram, 12 (10.3%) with a positive 2 cervigram, and 5 (4.3%) with a positive 3 cervigram. Of the 56 histologically confirmed cases of high-grade squamous intraepithelial lesions detected by cervicography, 8 (14.3%) were missed by all 3 cytologic screening methods.

**Sensitivity and specificity of cervicography compared with the referent diagnosis.** The sensitivity and specificity of cervicography for the detection of high-grade squamous intraepithelial lesions or cancer are presented by age group in Table IV. Considering the referral threshold for cervicography of any positive cervigram (P0 to P3), the overall sensitivity for high-grade squamous intraepithelial lesions and cancer was 49.3% (95% confidence interval 40.9%-57.7%), the specificity was 95.0% (95% confidence interval 94.5%-95.5%), and the positive predictive value was 13.8% (95% confidence interval 10.8%-16.9%). The sensitivity fluctuated between 36% and 75% in age groups <50 years old. A drop in sensitivity was observed in women ≥50 years old. When women were categorized as younger than 50 years and ≥50 years old, the sensitivities of cervicography were 54.6% and 26.9%, respectively ($\chi^2 = 6.4$; $P = .01$).

The reduction in sensitivity in the older age groups was related to menopausal status. Among all women, cervicography yielded a sensitivity of 30.0% in women who were no longer having menstrual periods, compared with a sensitivity of 54.7% in women who were still having menstrual periods. In stratified analyses, menopausal status appeared to be the major predictor of cervicography sensitivity, to the extent that the closely associated variables of age and menopausal status could be disentangled. The performance of cervicography did not appear to be meaningfully affected by hormonal contraceptive use, smoking, or having a previous abnormal Papanicolaou smear, once menopausal status and age were taken into account.

For readers who are interested in the detection of low-grade squamous intraepithelial lesions by cervicography, Table V presents the sensitivity and percent referral data, where disease is defined as low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, or cancer. The results closely parallel the performance for detection of high-grade squamous intraepithelial lesions and cancer previously shown in Table IV.

**Conventional cytologic screening compared with referent diagnosis.** As a point of reference, sensitivities and specificities were calculated for conventional cytologic

**Table IV.** Sensitivity and specificity of cervicography for detection of cancer, high-grade squamous intraepithelial lesion, or high-grade squamous intraepithelial lesion 2

| | | | *Threshold level* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | *Referred by cervicography if atypical or more severe* | | | *Referred by cervicography if P0 or more severe* | | |
| | *No. HSIL or cancer* | *Total* | *Sensitivity (%)* | *Specificity (%)* | *Positive predictive value (%)* | *Sensitivity (%)* | *Specificity (%)* | *Positive predictive value (%)* |
| Overall | 136 | 8460 | 62.5 | 85.0 | 6.4 | 49.3 | 95.0 | 13.8 |
| Age group* | | | | | | | | |
| 18-24 y | 13 | 1043 | 92.3 | 73.7 | 4.2 | 53.9 | 91.8 | 7.7 |
| 25-29 y | 23 | 1274 | 52.2 | 78.8 | 4.3 | 39.1 | 93.1 | 9.5 |
| 30-34 y | 33 | 1336 | 81.8 | 82.4 | 10.5 | 69.7 | 95.5 | 28.1 |
| 35-39 y | 25 | 1170 | 52.0 | 83.6 | 6.5 | 36.0 | 95.6 | 15.3 |
| 40-49 y | 16 | 1604 | 81.3 | 88.5 | 6.6 | 75.0 | 95.7 | 15.0 |
| 50-64 y | 10 | 1293 | 30.0 | 94.7 | 4.2 | 30.0 | 96.8 | 6.8 |
| ≥65 y | 16 | 740 | 31.3 | 93.5 | 9.6 | 25.0 | 96.0 | 12.1 |
| Still having menstrual periods | | | | | | | | |
| Yes | 106 | 6264 | 69.8 | 81.7 | 6.2 | 54.7 | 94.5 | 14.6 |
| No | 30 | 2196 | 36.7 | 94.4 | 8.3 | 30.0 | 96.5 | 10.5 |

Referent diagnosis is used as the gold standard diagnosis (Table II). Women with technically defective cervigrams were reported with cervigram results of negative (n = 113) and are included in this analysis. *HSIL,* High-grade squamous intraepithelial lesion.
*Age group was established on the basis of the date of enrollment interview.

evaluation compared with the referent diagnosis. Using a threshold diagnosis of atypical squamous cells of undetermined significance or more severe to determine a positive cytologic test result and a disease definition of high-grade squamous intraepithelial lesion or more severe, 586 of the 8449 women (6.9%) with available cytologic test results were referred for colposcopy by conventional cytologic evaluation, yielding a sensitivity of 77.2% and a specificity of 94.2%. Sensitivities were 75.5% and 84.6% among women younger than 50 years of age and 50 years of age and older, respectively. The association between age group (<50 vs ≥50) and cytologic sensitivity for high-grade squamous intraepithelial lesions and cancer was not statistically significant ($\chi^2 = 0.995$; $P = .32$). Where the disease definition was loosened to a referent diagnosis of low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, or cancer, conventional cytologic evaluation yielded a sensitivity of 67.7%, with the same 6.9% of women screened being referred for colposcopy.

**Cervicography compared with conventional cytologic evaluation on the referent diagnosis.** Cervicography and conventional cytologic test results were compared directly by assessing the referent diagnosis in cases in which cervicography and cytologic evaluation yielded discordant results on referral for colposcopy (Table VI). Of the 8284 participants who had technically adequate results for both tests, 884 (10.7%) had discordant referral recommendations. Specifically, 489 women (5.9%) were referred by conventional cytologic testing but not cervicography, whereas 395 women (4.8%) were referred by cervicography and not by conventional cytologic evaluation.

Considering the 395 women with discrepant results who were referred by cervicography, 1 (0.3%) had a referent diagnosis of cancer, 15 (3.8%) had histologically confirmed high-grade squamous intraepithelial lesions, 30 (7.6%) had histologically confirmed low-grade squamous intraepithelial lesions, and 13 (3.3%) had non–histologically confirmed low-grade squamous intraepithelial lesions. Of the 489 women who were referred by conventional cytologic evaluation and not by cervicography, none had a referent diagnosis of cancer, 47 (9.6%) had histologically confirmed high-grade squamous intraepithelial lesions, 5 (1.0%) had non–histologically confirmed high-grade squamous intraepithelial lesions, 16 (3.3%) had histologically confirmed low-grade squamous intraepithelial lesions, and 75 (15.3%) had non–histologically confirmed low-grade squamous intraepithelial lesions.

Of the 131 women with high-grade squamous intraepithelial lesions or cancer with adequate screening results by both methods, 52 (39.7%) were referred for colposcopy by conventional cytologic evaluation and not by cervicography and 16 (12.2%) were referred by cervicography and not by cytologic evaluation. The superior sensitivity of cytologic testing was statistically significant (McNemar's $\chi^2 = 19.1$; $P < .001$), but only cervicography detected every case of invasive cancer.

**Cervicography compared with conventional cytologic evaluation on HPV status.** Apart from the referent diagnosis, another independent standard is detection of HPV using DNA testing. The severity of both cervicographic and conventional cytologic diagnoses were strongly associated with increasing DNA positivity for cancer-associated

**Table V.** Sensitivity and percent referred for colposcopy by cervicography, for detection of cancer, HSIL, HSIL2, LSIL, or LSIL2

| | | | *Threshold level* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | *Referred by cervicography if atypical or more severe* | | | *Referred by cervicography if P0 or more severe* | | |
| | *No. LSIL, HSIL, or cancer* | *Total* | *Sensitivity (%)* | *Percent referred* | *Positive predictive value (%)* | *Sensitivity (%)* | *Percent referred* | *Positive predictive value (%)* |
| Overall | 325 | 8460 | 57.5 | 15.8 | 14.0 | 41.2 | 5.7 | 27.7 |
| Age group* | | | | | | | | |
| 18-24 y | 67 | 1043 | 70.2 | 27.1 | 16.6 | 43.3 | 8.7 | 31.9 |
| 25-29 y | 64 | 1274 | 54.7 | 21.7 | 12.6 | 43.8 | 7.5 | 29.5 |
| 30-34 y | 63 | 1336 | 63.5 | 19.2 | 15.6 | 47.6 | 6.1 | 36.6 |
| 35-39 y | 55 | 1170 | 49.1 | 17.2 | 13.4 | 32.7 | 5.0 | 30.5 |
| 40-49 y | 42 | 1604 | 64.3 | 12.2 | 13.8 | 47.6 | 5.0 | 25.0 |
| 50-64 y | 15 | 1293 | 40.0 | 5.5 | 8.5 | 33.3 | 3.4 | 11.4 |
| ≥65 y | 19 | 740 | 26.3 | 7.0 | 9.6 | 21.1 | 4.5 | 12.1 |
| Still having menstrual periods | | | | | | | | |
| Yes | 287 | 6264 | 60.6 | 19.2 | 14.5 | 42.9 | 6.4 | 30.9 |
| No | 38 | 2196 | 34.2 | 6.1 | 9.8 | 29.0 | 3.9 | 12.8 |

Referent diagnosis is used as the gold standard diagnosis (Table II). Women with technically defective cervigrams were reported with cervigram results of negative (n = 113) and are included in this analysis. *HSIL,* High-grade squamous intraepithelial lesion; *LSIL,* low-grade squamous intraepithelial lesion.

*Age group was established on the basis of the date of enrollment interview.

HPV types ($\chi^2$ for trend for cervicography = 178.4; $P < .001$; $\chi^2$ for trend for cytologic testing = 802.3; $P < .001$). For example, cancer-associated HPV DNA was found in 440 of 7000 women (6.3%) who had a negative result on cervigram, 99 of 850 women (11.6%) who had atypical cervigram results, 8 of 144 women (5.6%) with a positive 0 cervigram, 64 of 290 women (22.1%) with a positive 1 cervigram, 13 of 32 women (40.6%) with a positive 2 cervigram, and 8 of 18 women (44.4%) with a positive 3 cervigram.

Of the 395 women who were referred for colposcopy by cervicography but not by cytologic evaluation, 34 (8.6%) had a positive test result for a cancer-associated HPV type. Of the 488 women who were referred for colposcopy by cytologic evaluation but not by cervicography, 149 (30.5%) had a positive test result for a cancer-associated HPV type. The higher HPV DNA prevalence in the additional "pick-ups" by cytologic testing was statistically significant (McNemar's $\chi^2 = 72.3$; $P < .001$).

## Comment

In this high-risk, population-based study, an abnormal result on cervigram led to the referral of 5.7% of women for colposcopy, resulting in detection of all cancers and 49.3% of all high-grade lesions and invasive cancers combined. The specificity of cervicography was 95.0%, with a positive predictive value of 13.8%. The sensitivity of cervicography was markedly reduced in postmenopausal women.

The importance of different levels of positive cervigrams varied. We observed that positive 2 and especially positive 3 diagnoses by cervicography had high positive predictive value, in that a majority of women given these diagnoses were found to have underlying squamous intraepithelial lesions. However, these diagnoses were rather uncommon and insensitive. A screening program could not restrict colposcopic referral to these diagnoses because the positive 1 diagnostic category was important to the detection of underlying high-grade squamous intraepithelial lesions and cannot be ignored. The positive 0 category also must be taken seriously, although the overwhelming majority of women given this diagnosis were normal such that the HPV DNA positivity is even lower than among women with normal cervigrams. The diagnosis of positive 0 identified 3 of the 11 women with referent diagnoses of cancer, 2 of whom were also detected by unaided visual inspection.

Using an even more liberal diagnostic threshold of atypical or positive to define a positive cervigram would permit cervicography to achieve greater sensitivity, but at the expense of a reduced specificity. This potential for cervicography to be nonspecific, referring an unacceptably high percentage of normal women, was seen in earlier screening studies.[17-19] Previous studies of cervicography showed mixed results and were limited by their inclusion of selected populations; small sample size; and earlier, nonspecific criteria for diagnostic classification.[17-24] Using positive cervigram results as the referral threshold has made the screening system much more viable from a referral point of view, as indicated by its high specificity. If sensitivity for high-grade squamous intraepithelial lesions could be increased without greatly increasing referrals, the method would be promising because of its ease and low rate of technically defective tests.

**Table VI.** Category of agreement on colposcopic referral by referent diagnosis

| | *Category of agreement on colposcopic referral†* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Cervicography not referred–cytology not referred* | | *Cervicography not referred–cytology referred* | | *Cervicography referred–cytology not referred* | | *Cervicography referred–cytology referred* | | |
| *Final diagnosis** | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* | *Total* |
| Normal | 6571 | 89.9 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 6571 |
| Normal 2 (differential diagnosis of ASCUS vs normal) | 540 | 7.4 | 131 | 26.8 | 5 | 1.3 | 1 | 1.2 | 677 |
| Equivocal—Cervigram | 0 | 0.0 | 0 | 0.0 | 321 | 81.3 | 9 | 10.3 | 330 |
| Equivocal—Papanicolaou smear | 8 | 0.1 | 171 | 35.0 | 0 | 0.0 | 1 | 1.2 | 180 |
| Equivocal—ThinPrep | 132 | 1.8 | 9 | 1.8 | 1 | 0.3 | 0 | 0.0 | 142 |
| Equivocal—NL/LSIL (overall results equivocal) | | | | | | | | | |
| Equivocal—NL/HSIL (differential diagnosis of HSIL vs negative) | 4 | <0.1 | 3 | 0.6 | 2 | 0.5 | 0 | 0.0 | 9 |
| LSIL 2 (not histologically confirmed) | 16 | 0.2 | 75 | 15.3 | 13 | 3.3 | 11 | 12.6 | 115 |
| LSIL (histologically confirmed) | 14 | 0.2 | 16 | 3.3 | 30 | 7.6 | 13 | 14.9 | 73 |
| HSIL 2 (not histologically confirmed) | 1 | <0.1 | 5 | 1.0 | 0 | 0.0 | 0 | 0.0 | 6 |
| HSIL (histologically confirmed) | 12 | 0.2 | 47 | 9.6 | 15 | 3.8 | 40 | 46.0 | 114 |
| Cancer | 0 | 0.0 | 0 | 0.0 | 1 | 0.3 | 10 | 11.5 | 11 |
| TOTAL | 7313 | | 489 | | 395 | | 87 | | 8284 |

*ASCUS,* Atypical squamous cells of undetermined significance; *HSIL,* high-grade squamous intraepithelial lesion; *LSIL,* low-grade squamous intraepithelial lesion.

*Definitions of the referent diagnosis are provided in Table II.

†Colposcopic referral based on cervigram and conventional cytology results according to the following criteria: Women were referred for colposcopy by cervicography if cervigrams were positive (positive 0, positive 1, positive 2, positive 3); women were referred for colposcopy by conventional cytology if smears were classified as ASCUS or more severe; data for participants with either technically defective cervigrams (n = 113) or unsatisfactory conventional cytology (n = 57), or both (n = 4), were excluded from this analysis; cytologic results were missing for 5 participants (1 of whom also had a technically defective cervigram); conventional cytologic testing was not done for 6 participants. Cervigram classification scheme is provided in Table I.

Regardless of referral threshold, cervicography may not be beneficial to postmenopausal women. A marked reduction in the sensitivity of cervicography was seen in women who were no longer having menstrual periods and probably can be explained by associated positional change in the transformation zone. Most cervical neoplasia occurs at the transformation zone, which moves cephalad into the endocervical canal as a woman ages. Because cervicography enables the evaluator to visualize a projected image of the cervix, the cervigram evaluator cannot detect lesions far inside the endocervical canal. Our data would strongly suggest restriction of cervicography to premenopausal women.

As a point of comparison, optimized conventional cytologic screening resulted in 6.9% of women being referred for colposcopy. Cytologic screening resulted in 77.2% of women with high-grade squamous intraepithelial lesions or cancer having a correct diagnosis and 94.2% of women without high-grade squamous intraepithelial lesions or cancer being correctly identified as not having disease. Conventional cytologic screening resulted in higher sensitivity than cervicography (except for invasive cancer), with only a very small difference in specificity between the 2 screening methods. However, conventional cytologic evaluation in this study had unusually high sensitivity for high-grade squamous intraepithelial lesions and cancer compared with much less successful performance in Guanacaste Province in the past.[25] Cancer rates have remained extremely high in Guanacaste for many years despite existing screening services. The maintenance of a highly accurate conventional cytologic screening program is labor-intensive and technically difficult. The quality of cytologic evaluation in our study was optimized by careful clinician training, a strict fixation and staining protocol, and site visits by experts in cytotechnology and cytopathology from the United States. Still, improvement of existent conventional cytologic evaluation should be considered along with other options for long-term cervical cancer prevention programs.

When cervicography and conventional cytologic diagnoses differed regarding the need for colposcopy, an analysis of the discordant results provided information about the performance of one screening method compared with the other. More than 3 times as many cases of high-grade squamous intraepithelial lesions and cancer were detected by cytologic testing alone than were detected by cervicography alone, but cervicography identified 1 cancer that cytologic evaluation missed. However, 6 of 11 cancers (54.5%) were evident on clinical examination and these women would have been referred on that basis alone. Moreover, significantly more women who were referred only by conventional cytologic evaluation

had a positive DNA test result for cancer-associated HPV types than women who were referred only by cervicography. This difference suggests that the additional sensitivity provided by cytologic testing represented detection of additional true positive squamous intraepithelial lesions, not false positives. Cancer-associated HPV types were detected more frequently in women with referent diagnoses of equivocal than in women with referent diagnoses of normal, indicating that some women with diagnoses of equivocal likely had disease. It should be noted that the hybrid capture tube test used in our study has a low sensitivity (10 pg/mL) compared with the next generation of the test (Hybrid Capture II, 1 pg/mL).

The generalizability of this study is limited by the fact that it was conducted in a population with an age-adjusted rate of cervical cancer incidence averaging around 33 per 100,000. These rates are higher than the average for Costa Rica and 4 to 5 times higher than in the United States.[11] The performance of any screening test may differ in a population with a lower prevalence of disease. Cervicography is limited by its dependence on an expert, trained evaluator to interpret cervigrams. However, the same individuals collaboratively interpreted all cervigrams for this study, so interobserver variation should be minimal. Cervigram review is also subject to intraobserver variation. Strict controls on evaluator training and certification are in place to achieve high reproducibility among evaluators. Cervicography evaluation is much faster than conventional cytologic interpretation, which permits a large volume of screening dependent on fewer expert personnel.

A major strength of this study is the large, population-based sample in which it was conducted. This large sample size permitted the unbiased identification of a sufficiently large number of women with high-grade squamous intraepithelial lesions or invasive cancer to be able to assess the performance of screening methods in detecting this category of diagnosis separately from low-grade squamous intraepithelial lesions.

In summary, cytologic evaluation performed substantially better than cervicography for detecting high-grade squamous intraepithelial lesions in this high-risk population. However, cervicography appears particularly useful in detecting invasive cervical cancer and in screening for cancer precursors in regions without established, effective cytologic programs. In current work, we are examining whether the sensitivity of cervicography for detection of high-grade squamous intraepithelial lesions can be improved by further adjusting the diagnostic criteria.

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